Remarks

Upon entry of the foregoing amendment, claims 2, 3, 6, 8 and 11-14 are pending in the application. Claims 2, 6, and 8 have been amended to recite a Markush group. Claims 16-18 have been newly canceled. These changes are believed to introduce no new matter, and their entry is respectfully requested.

The Rejections

The Rejection under 35 U.S.C. § 112, first paragraph (enablement)

At Office action paragraph number 2, claims 16-18 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully traverse this rejection. However, in the interests of advancing prosecution, Applicants have canceled claims 16-18. Accordingly, this rejection can be withdrawn.

The First Rejection under 35 U.S.C. § 103

At Office action paragraph number 7, claims 2, 3, 6 and 8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Dittrich *et al., Phytochemistry 11*:245-250 (1971) (herein "Dittrich") in view of Sultana *et al., Phytochemistry 50*:1249-1253 (1999) (herein "Sultana") or Pagé (US 6,002,025; herein "Pagé") and Liu (US 5,969,165; herein "Liu").

Dittrich is relied on as teaching that the compound 5-*O*-methyl-*myo*-inositol (sequoyitol) is found in the *Taxaceae* class and family of plants. However, the Examiner states that Dittrich does not teach a method of extracting the compound from the plants.

The Examiner states that the steps and solvents disclosed in the claims are well known and are taught by Sultana and by Pagé and Liu. The Examiner states that Liu additionally teaches the use of a macroporous resin and that his resin allows for large industrial scale production.

The Examiner states that one of ordinary skill in the art at the time the invention was made would have found it obvious to extract the compound 5-*O*-methyl-*myo*-inositol from the *Taxaceae* class and family of plants as disclosed in Dittrich by using well known steps and solvents such a those taught by Sultana and Pagé and Liu.

Applicants respectfully traverse this rejection and request reconsideration.

Applicants submit that a *prima facie* of obviousness is not established. First, there is no rationale for one of ordinary skill in the art to combine the teachings of the cited documents. As acknowledged by the Examiner, Dittrich does not mention the isolation of sequoyitol. Rather, it only indicates in Table 1 that sequoyitol was detected in certain *Taxaceae* species. Sultana concerns isolation of two flavones, which are non-polar compounds, from *Melicope micrococca*, a plant that does not belong to the genus of *Taxaceae*. In addition, the amount of sequoyitol recovered in Sultana was low: only 18 mg sequoyitol was obtained from 242 g of starting material. Both Pagé and Liu concern the isolation of taxanes, a group of highly non-polar compounds, from certain *Taxus* species.

In contrast, the present claims are directed to a process of isolating sequoyitol, a highly polar compound, from *Taxaceae*. Industrially useful amounts can be recovered. A person of ordinary skill in the art at the time the invention was made, would have no

reason to consider it instructive to look into isolation methods designed for purification of compounds that have very different chemical properties or from a different source.

Furthermore, contrary to the Examiner's assertion, the alleged combination of the documents would not lead to the claimed process. Table 1 of Dittrich indicates that sequoyitol can be detected in *Taxaceae* and *Taxus baccata*. Dittrich also lists sequoyitol in a pathway on page 246 and suggests that sequoyitol as an intermediate in the pathway wherein *myo*-inositol is converted to sequoyitol, then to D-pinitol and then to D-1-O-methyl-mucoinositol. If this pathway is also present in *Taxaceae* and *Taxus baccata*, it may limit useful amounts of sequoyitol from being extracted from *Taxaceae* and *Taxus baccata* as the sequoyitol is only an intermediate in the pathway. Thus, there is a doubt that *Taxaceae* or *Taxus baccata* contain useful, extractable amounts of sequoyitol, or that this class can serve as a source for the same. Indeed, Dittrich is silent as to whether useful amounts of sequoyitol can be extracted from Dittrich's source, *Juniperus communis*, much less suggest a reason for extracting useful amounts of sequoyitol from a different source. As recognized by the Examiner, Dittrich does not provide a method for extracting sequoyitol from *Taxaceae*.

Furthermore, the claimed process is very different from that mentioned in the combination of Sultana, Pagé and Liu.

Sultana reported the isolation of sequoyitol from *Melicope micrococca*. Sultana used 242 g of Melicope micrococca, extracted first by Soxhlet with petroleum ether, EtOAc and MeOH. Then, the EtOAc extract was fractionated by vacuum liquid chromatography (VLC) on silica gel. The fraction that eluted with 15-20% MeOH in

EtOAc was then purified by column chromatography over silica gel to give only 18 mg of sequoyitol.

Pagé mentions that taxanes were purified by chromatographic separation using a phenylalkyl chromatographic resin, wherein the phenylalkyl moiety may be linked to silica or silicon-based resin, or other chromatography support. In contrast, Applicants used a macroporous resin (exemplified by D101), that is made of polystyrene. Macroporous chromatography is a molecular screening plus adsorption chromatography. However, Pagé used a phenylalkyl chromatographic resin, which is a distribution chromatography. In addition, the final products are different-taxanes are large non-polar diterpenes, while sequoyitol is a small polar compound.

Liu disclosed a method for obtaining taxane analogues from a source containing taxanes. Liu's method employs a polymeric resin column for separating non-polar taxane analogues (one kind of diterpenes). Liu used polymeric resin (Dowex™ resin, polystyrene-DVB) column chromatography. Dowex™ resin is a strong acid cation exchange resin (*see* Supplemental IDS document NPL14, previously submitted). In contrast, Applicants used a macroporous resin, made of polystyrene, exemplified by D101, to isolate polar sequoyitol. Macroporous chromatography is both a molecular screening and adsorption chromatography.

In summary:

1. Dittrich removed *myo*-inositol and sequyitol by cellulose column chromatography (eluted with acetone-H_2O=85:15), it does not mention to further purify sequoyitol.

2. Sultana used silica gel column chromatography to obtain low amount of sequyitol (only 18 mg). Silica gel column chromatography is a normal-phase chromatography, which is suitable for isolation of non-polar compounds, but not suitable for isolation of polar sequoyitol.

3. Pagé used phenylakyl chromatography resin for isolation of taxanes (non-polar diterpenes). Phenylalkyl chromatographic resin is suitable for isolation of non-polar taxanes (diterpenes), but not suitable for isolation of polar sequoyitol.

4. Liu used polymeric resin column chromatography (Dowex™ resin, polystyrene-DVB), which is a strong acid cation exchange resin, for isolation of non-polar taxanes. Dowex™ is suitable for isolation of non-polar taxanes (diterpenes), but not suitable for isolation of polar sequoyitol.

In contrast, the claimed method is different. *Inter alia*:

5. Applicants used macroporous resin (exemplified by D101) column chromatography for isolation of sequoyitol. The resin is suitable for isolation of sequoyitol. There is no suggestion to change the procedure in any of the cited documents or the combination of the art.

6. Applicants isolated sequoyitol in large scale. Among the cited documents, only Sultana isolated sequoyitol, but in a very small scale. There is no suggestion that Taxaceae would be a good source for sequoyitol or that sequoyitol could be produced in a scale greater than that presented by Sultana.

7. Additionally, the starting plant materials were different. None of Sultana, Dittrich, Pagé or Liu suggests that Taxaceae would be a good source of sequoyitol.

In fact, Applicants isolated active compounds from *Taxaceae* by following the anti-diabetic activity and crystallized the compound. The structure of the isolated active compound was determined to be sequoyitol (5-*O*-methyl-*myo*-inositol).

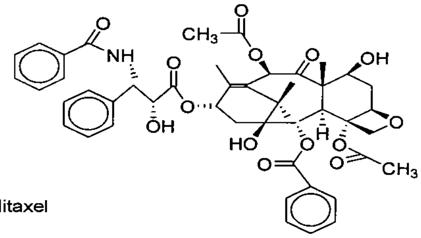
The Examiner states that the steps and solvents disclosed in the claims are well known and are taught by Sultana and by Pagé and Liu, thus the claims are allegedly obvious. However, the Supreme Court stated in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), "a patent composed of several elements *is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.*" *KSR*, 127 S. Ct. at 1741. As explained above, since the cited documents are directed to isolating compounds of different properties and using different starting materials, the teachings at most provide an unlimited numbers of possible ways that can be experimented in order to isolate sequoyitol.

The discussion above demonstrates that the claimed method is not rendered obvious by the combination of the cited art. The solution to the problem to be solved - the extraction of useful amounts of sequoyitol from a natural source - as well as the need for a new protocol to achieve such extraction assuming such a source rich in extractable sequoyitol can be identified, which resulted in the claimed method, are not reached by the combination of the cited art. Applicants have shown that the claimed method is not merely substitution of one known element for another to obtain a predictable result.

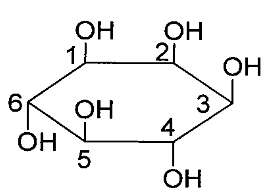
There is no evidence that one of ordinary skill in the art would have recognized that applying the extraction procedure as recited in claim 1 to *Taxus spp.* would have yielded Applicants' results and resulted in an improved extraction method. In fact, it was not predictable that Applicants' combination of elements that results in the claimed method would yield the results that Applicants obtained.

At Office Action paragraph 9, the Examiner asserts that based on Dittrich, one of ordinary skill in the art would have a reasonable expectation that *Taxaceae* plants are a good source for sequoyitol and the compound can be extracted from them. However, Dittrich only indicate that sequoyitol is "detectable" in the three *Taxaceae* species listed in Table 1. The hot water extracts were used for the detection. There is no indication that *Taxaceae* would be a good source from which to purify sequoyitol.

The Examiner acknowledges that neither Sultana nor Pagé mentions the type of chromatography used in the claimed process, but asserts that Liu provides the motivation for using a macroporous resin. Applicants disagree. Liu focus on isolation and purification of taxanes (*e.g.*, paclitaxel, *see* below left for its structure), a group of non-polar compounds that have very differ chemical and physical properties from sequoyitol, which is polar. (*see* below right for its structure) A skilled artisan would have no reason to believe, based on Liu's teachings, that a macroporous resin would likely to work for isolating sequoyitol, let alone for a large scale production.



paclitaxel



myo-Inositol

The Examiner further argues that Pagé shows that taxanes have been obtained from the bark and needles of different *Taxus* species by using steps such as extraction, chromatography and crystallization, and that solvents such as methanol and ethanol were known for extraction. However, major differences would have been expected between isolation of Taxanes and sequoyitol due to structural and property differences. In addition, Taxanes had been successfully purified from certain species of *Taxus*. In indeed, Pagé only focuses on separation of taxanes from each other. *See* Pagé, col. 2, line 8. In contrast, none of the cited documents suggests that useful amounts of sequoyitol may be extracted from *Taxus*. Thus, success in purification of taxanes does not lead a person of ordinary skill in the art to isolate sequoyitol from *Taxus* with a reasonable expectation of success.

The discussion above shows that the Examiner's articulated reasoning is not supported by a sufficient rational underpinning to support a legal conclusion of obviousness. Accordingly, *prima facie* obviousness is not established and this rejection can be withdrawn.

The Second Rejection under 35 U.S.C. § 103

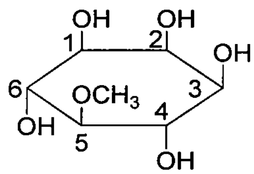
At Office Action paragraph number 8, claims 11-14 and 16-18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ostlund (US 5,550,166; herein "Ostlund") in view of Dittrich and Oberley (online Pubmed abstract for *Free Radic. Biol. Med.* 5:113-124 (1988); herein "Oberley").

Solely in the interests of advancing prosecution, Applicants have canceled claims 16-18. Accordingly, the rejection of claims 16-18 are moot.

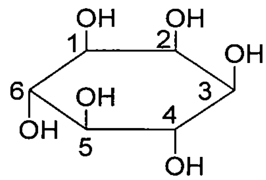
Ostlund is relied on as teaching the compound pinitol, compositions containing pinitol and its use in the treatment of diabetes. Dittrich is relied on as teaching that pinitol is a stereoisomer of sequoyitol. Oberley is relied on as teaching that not only are oxygen radicals involved in the cause of diabetes but also that they appear to play a role in some of the complications seen in long-term treatment of diabetes. Examiner states that one having ordinary skill in the art at the time the invention was made would have found it obvious to utilize 5-O-methyl-*myo*-inositol (sequoyitol) in a composition for the treatment of diabetes, as taught by Ostlund, because compounds that are stereoisomers are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. Applicants respectfully traverse this rejection.

Compounds that are similar in structure may possess different properties. For example, D-pinitol and L-pinitol are very similar in structure. However, they have different properties. For example, D-pinitol's $[\alpha]_D^{20} = +67°$ (c 2.5 in H_2O), but L-pinitol's $[\alpha]_D^{20} = -65°$ (c 2, in H_2O). Also, their bio-activities are quite different: L-pinitol shows antifungal activity (*see* Supplemental IDS document NPL18), while D-pinitol is alleged to show hypoglycemic and antidiabetic activity.

In another example, while myo-inositol and sequoyitol have the same structural nucleus (*myo*-inositol), myo-inositol shows vitamin B complex and lipotropic activities (see Supplemental IDS document NPL20, previously submitted).



5-*O*-Methyl-*myo*-inositol



myo-Inositol

As an additional example, it is well known that only L-amino acids are incorporated in proteins in human, while the stereo-isomers, D-amino acids, although have very similar structure, are not incorporated into proteins in humans. *See* Donald Voet and Judith G. Voet, *Biochemistry*, p. 68 (1990), submitted herewith as Exhibit A.

Furthermore, at the time the invention was made, there were conflict teachings in the art regarding whether pinitol could alter basal glucose and lipid kinetics or the effect of insulin on glucose and lipid metabolism. For example, Davis, A. *et al.*, *Diabetes Care 23*: 1000-1005 (2000), (*see* Supplemental IDS document NPL17, previously submitted, herein "Davis") reported that pinitol treatment did not increase insulin sensitivity in obese individuals with mild type 2 diabetes. Davis reports a double blind trial with twenty-two subjects where the subjects were given either a placebo or soybean-derived pinitol. After 28 days, the researchers found that the pinitol treatment did not change baseline glucose production, insulin-mediated glucose disposal, or rates of appearance of free fatty acids and glycerol in plasma. At page 1004, column 1, last paragraph, the authors state that the "results of the present study do not support a beneficial effect of inositol therapy on insulin sensitivity in diabetic subjects." Applicants respectfully point out that one of the authors of the Davis is Ostlund, RE Jr., who is also a co-inventor of the Ostlund '166 patent that is cited by the Examiner in this rejection. Additionally, Davis was published in 2000, 4 years after the '166 patent was issued, reporting

conflicted observations regarding the alleged anti-diabetic function of pinitol by one of the inventors of the '166 patent.

Moreover, Campbell, W.W. *et al.*, *FASEB J. 16* (4 part 1): A24 (abstract) (2002), (Supplemental IDS document NPL15, previously submitted), administered oral pinitol to older people (average age 66±8 yr). The authors conclude that "These data suggest that oral pinitol supplementation does not influence glucose, insulin or C-peptide responses to oral or intravenous glucose challenges in older people." This report was later expanded and published as a paper that also had Ostlund as a co-author (*see* Supplemental IDS document NPL16, previously submitted, Campbell, W.W. *et al., J. Nutr. 134*: 2998-3003 (2004)).

The focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge. (*See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57526, 57527 (October 10, 2007), column 3, first full paragraph). The above-discussed facts demonstrate that at the time when the present application was filed, one of an ordinary skill in the art would not have reasonably believed that any *myo*-inositol, and especially, Applicants' specific compound, sequoyitol (5-*O*-methyl-*myo*-inositol), would have anti-diabetic effects based on the stereoisomer relationship with pinitol and certain reports of pinitol's alleged anti-diabetic functions.

The evidence above establishes that at the time of the invention, there were clinical studies that had been published that detracted from the teachings of Ostlund, in a manner that was not cured by the combination of the teachings of Dittrich and Oberley. Applicants have shown that the person of ordinary skill in the art had reasons to doubt the teachings of Ostlund, as relied on by Examiner, as to the compound pinitol, and thus had no reason to extend Ostlund to a different compound. Thus, the combination of Dittrich and Oberley and Ostlund does not reach the claimed invention, and does not render it *prima facie* obvious.

At Office Action paragraph 9, the Examiner asserts that that neither Davis nor Campbell negate the teaching of Ostlund. Applicants submit that conflict results regarding the alleged anti-diabetic properties of pinitol observed by these studies raise a question as to whether pinitol exerted insulin-like properties. This is especially true given the fact that Ostlund, an inventor of the '166 patent that was cited against the present claims, was also involved in the studies reported in Davis and Campbell. Additionally, there are numerous examples of stereoisomers that do not share functional similarities (*e.g.*, L-amino acids and D-amino acids). Furthermore, Dittrich and Oberley are silent with regard to whether pinitol and sequoyitol would share this characteristic. Thus, a person of ordinary skill in the art, at the time of filing the present application, would not have reached the claimed invention based on the teachings of the combination of Dittrich, Oberley and Ostlund. Accordingly, the claims are not *prima facie* obvious.

The Examiner also states that Plourde does not indicate that inositol derivatives needed to be in the disaccharide form to have insulin-like effects. However, Plourde states that synthetic insulin-mimetic substances that are active contain a nonacetylated

glucosamine moiety glycosidically linked to a phosphorylated inositol (*i.e.*, in the disaccharide form). *See* Plourde, p. 2607, left column.

The evidence presented herewith, and the discussion above shows that the Examiner's articulated reasoning is not supported by a sufficient rational underpinning to support a legal conclusion of obviousness. Accordingly, *prima facie* obviousness is not established and this rejection can be withdrawn. Accordingly, this rejection can be withdrawn.

Conclusion

Prompt and favorable consideration of this amendment and reply is respectfully requested. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided, or to send an e-mail at the e-mail address provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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Exhibit A: Donald Voet and Judith G. Voet, Biochemistry, P. 68
(John Wiley & Sons, 1990)

BIOCHEMISTRY

DONALD VOET
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JUDITH G. VOET
Swarthmore College

Illustrators:
IRVING GEIS
JOHN AND BETTE WOOLSEY

WILEY
JOHN WILEY & SONS
New York • Chichester • Brisbane • Toronto • Singapore

To:

Our parents, who encouraged us,
Our teachers, who enabled us, and
Our children, who put up with us.

Cover Art: One of a series of color studies of horse heart cytochrome *c* designed to show the influence of amino acid side chains on the protein's three-dimensional folding pattern. We have selected this study to symbolize the discipline of biochemistry: Both are beautiful but still in process and hence have numerous "rough edges." Drawing by Irving Geis in collaboration with Richard E. Dickerson.

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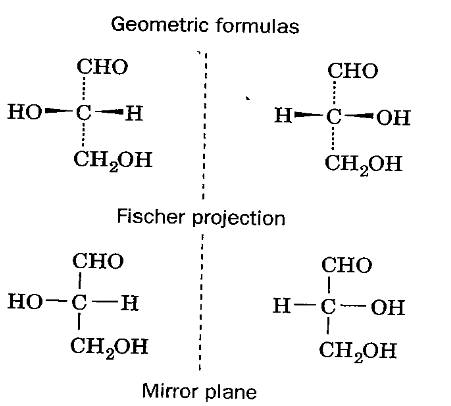
tions of −86.2, −10.4, and +12.5°C, respectively. Their enantiomers exhibit values of $[\alpha]_D^{25}$ of the same magnitude but of opposite sign. As might be expected from the acid–base nature of the amino acids, these quantities vary with the solution pH.

A problem with this operational classification system for optical isomers is that it provides no presently interpretable indication of the **absolute configuration** (spatial arrangement) of the chemical groups about a chiral center. Furthermore, a molecule with more than one asymmetric center may have an optical rotation that is not obviously related to the rotatory powers of the individual asymmetric centers. For this reason, the following relative classification scheme is more useful.

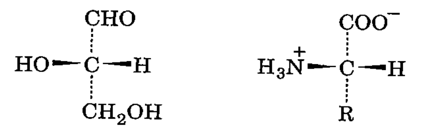
B. The Fischer Convention

In this system, the configuration of the groups about an asymmetric center is related to that of **glyceraldehyde,** a molecule with one asymmetric center. By a convention introduced by Emil Fischer in 1891, the (+) and (−) stereoisomers of glyceraldehyde are designated **D-glyceraldehyde** and **L-glyceraldehyde,** respectively (note the use of small upper case letters). With the realization that there was only a 50% chance that he was correct, Fischer assumed that the configurations of these molecules were those shown in Fig. 4-11. Fischer also proposed a convenient shorthand notation for these molecules, known as **Fischer projections,** which are also given in Fig. 4-11. In the Fischer convention, horizontal bonds extend above the plane of the paper and vertical bonds extend below the plane of the paper as is explicitly indicated by the accompanying geometrical formulas.



L-Glyceraldehyde **D-Glyceraldehyde**

Figure 4-11
The Fischer convention configurations for naming the enantiomers of glyceraldehyde as represented by geometric formulas (*top*) and their corresponding Fischer projection formulas (*bottom*). Note that in Fischer projection, all horizontal bonds point above the page and all vertical bonds point below the page. The mirror planes relating the enantiomers are represented by a vertical dashed line.



L-Glyceraldehyde **L-α-Amino Acid**

Figure 4-12
The configurations of L-glyceraldehyde and L-α-amino acids.

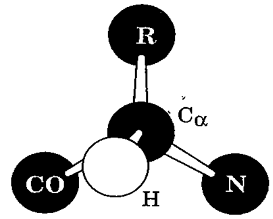


Figure 4-13
The "corncrib" mnemonic for the hand of L-amino acids. Looking at the C_α atom from its H atom substituent, its other substituents should read **CO—R—N** in the clockwise direction as shown. Here CO, R, and N, respectively, represent the carbonyl group, side chain, and main chain nitrogen atom. [After Richardson, J. S., *Adv. Protein Chem.* **34,** 171 (1981).]

The configuration of groups about a chiral center can be related to that of glyceraldehyde by chemically converting these groups to those of glyceraldehyde using reactions of known stereochemistry. For α-amino acids, the arrangement of the amino, carboxyl, R, and H groups about the C_α atom is related to that of the hydroxyl, aldehyde, CH_2OH, and H groups, respectively, of glyceraldehyde. In this way, L-glyceraldehyde and L-α-amino acids are said to have the same relative configurations (Fig. 4-12). Through the use of this method, the configurations of the α-amino acids can be described without reference to their specific rotations.

All α-amino acids derived from proteins have the L-stereochemical configuration; that is, they all have the same relative configuration about their C_α atoms. In 1949, it was demonstrated by a then new technique in X-ray crystallography that Fischer's arbitrary choice was correct: The designation of the relative configuration of chiral centers is the same as their absolute configuration. The absolute configuration of L-α-amino acid residues may be easily remembered through the use of the "corncrib" mnemonic that is diagrammed in Fig. 4-13.

Diastereomers Are Chemically and Physically Distinguishable

A molecule may have multiple asymmetric centers. For such molecules, the terms **stereoisomers** and **optical isomers** refer to molecules with different configurations about at least one of their chiral centers, but which are otherwise identical. The term enantiomer still refers